REMARKS

Claims 170-224 are pending and under consideration. With this Amendment, claims 3, 6-8, 10-13, 15-16, 19-21, 23-31, 33, 35-38, 45-46, 48-51, 120-13, and 153-169 are being canceled without prejudice against their reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications, and claims 170-224 are being newly added.

Correspondence between new claims 170-224 and the canceled claims is set forth in the following table:

Canceled Claim Number	New Claim Number
153	170
154	171
155	172
156	173
157	174
23	175
24	176
25	177
26	178
27	179
28	180
29	181
30	182
31	183
33	184
35	185
36	186
37	187
38	188
13	189
158	190
15	191
16	192
3	193
159	194
7	195
8	196
10	197
11	198
12	199
45	200
46	201
48	202
49	203
50	204

Canceled Claim Number	New Claim Number
51	205
160	206
161	207
162	208
163	209
164	210
165	211
166	212
169	213-219
-	220
120	221
121	222
122	223
123	224

New claim 170 recites that the claimed oligonucleotide compound consists of 12-50 monomers where adjacent monomers are linked together by a phosphate linkages or a phosphorothioate group, wherein the compound comprises a region of at least 8 contiguous monomers, one of which is a nucleoside analogue, and wherein the sequence of the region is identically present in SEQ ID NO: 130. Support for claim 170 can be found in canceled claim 153 and throughout the specification, and in particular at page 11, lines 23-26; page 12, lines 1-5 and 17-36; page 13, line 3; page 14, lines 18-21; page 31, lines 21-27; and page 85.

New claim 171 recites that the nucleoside analogue present in the region of the oligonucleotide of claim 170 is selected from the recited group of analogues having non-naturally occurring sugars. Support for claim 171 can be found in canceled claim 154 and throughout the specification, for example at page 12, lines 1-5 and 17-23; page 13, Scheme 1; page 38, lines 25-35; and page 85. New claim 172 recites that the nucleoside analogue is an LNA monomer. Support for new claim 172 can be found in canceled claim 155 and throughout the specification, for example at page 12, lines 17-23. New claims 173 and 174 recite that the LNA monomer is selected from the specifically recited LNA monomers. Support for new claims 173 and 174 can be found respectively in canceled claims 156 and 157 and throughout the specification, for example at page 12, lines 17-23; page 13, line 10-page 14, line 8; and page 21, lines 22-23.

New claims 175-186 recite the number of nucleoside analogues in the claimed compound. Support for new claims 175-186 can be found respectively in canceled claims 23-31, 33 and 35-36, and throughout the specification, for example at page 20, lines 3-19; and page 85. New claims 187 and 188 respectively recite that all monomers in the claimed compound are nucleoside analogues, and that the

monomer at the 3'-end of the claimed oligonucleotide compound is a DNA monomer. Support for new claims 187 and 188 can be found respectively in canceled claims 37 and 38 and throughout the specification, for example at page20, line 26 and at page 22, lines 23-31. New claims 189-192 recite the number of contiguous monomers that are present in the region of the claimed oligonucleotide compound of claim 170, wherein the sequence of the region is identically present in SEQ ID NO: 130. Support for new claims 189-192 can be found respectively in canceled claims 13, 158, 15 and 16, in claims 13-16 and originally filed, and throughout the specification, for example, at page 17, lines 18-23. New claims 193-199 recite the number of linked monomers present in the claimed oligonucleotide compound of claim 170. Support for new claims 193-199 can be found respectively in canceled claims 3, 159, and 7-12, and in the specification, for example at page 17, lines 10-16.

New claims 200 and 201 recite the nature of the linkage group between the monomers of the claimed oligonucleotide compound. Support for these amendments can be found respectively in canceled claims 45 and 46, and throughout the specification, for example at page 17, lines 25-33; page 21, line 33-page 22, line 3; and page 85. New claims 202-205 recite the number and arrangement of nucleosides and nucleoside analogues comprising the claimed compounds. Support for these amendments can be found respectively in canceled claims 48-51 and throughout the specification, for example at page 11, lines 28-31; page 22, line 23-page 23, line 24; page 24, lines 14-19; and page 85.

New claims 206-212 recite the sequence and chemical structure of the region of the claimed oligonucleotide compound of claim 170 or of the claimed oligonucleotide compound of claim 170. Support for new claims 206-212 can be found respectively in canceled claims 160-166, and throughout the specification, for example at page 17, lines 18-23, and at page 85, SEQ ID NO: 130.

New claims 213-219 recite that any cytosine in each cytosine-containing LNA monomer is 5-methyl cytosine. Support new claims 213-219 can be found in canceled claim 169, and throughout the specification, in particular at page 32, line 38; page 84, lines 5-6; page 35, lines 12-15; and page 85. New claim 220 recites a particular species of oligonucleotide compound of claim 170. Support for this claim can be found throughout the specification and in particular at page 84, lines 5-6 and page 85, SEQ ID NO: 130B.

New claims 221-224 recite conjugates and pharmaceutical compositions comprising an oligonucleotide compound of claim 170. Support for these amendments can be found respectively in canceled claims 120-123 and in the specification, for example, at page 12, lines 25-36.

No new matter has been added by way of these amendments.

Amendments of the Specification

The title has been amended to include the word "of" between "modulation" and "survivin". No new matter has been added by way of this amendment.

Allowable Subject Matter

The Examiner has indicated that claims 19-21 and 160-169 are free of the prior art, and therefore are allowable. The subject matter of claims 19-21 has been incorporated into new claims 170, 200 and 201.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 6-8, 10-12 and 35-38 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner contends that each of these claims depends from a canceled claim.

Claims 6-8, 10-12 and 35-38 have been canceled, and the subject matter incorporated into new claims 195-199, and 185-188. *See* claim correspondence chart, above. Each of new claims 195-199 and 185-188 depends from a pending claim and further limits the scope of the claim from which it depends.

Applicants therefore submit that none of the pending claims is indefinite. Reconsideration of the claims and withdrawal of the rejection thereof under 35 U.S.C. § 112, second paragraph is requested.

Rejections Under 35 U.S.C. § 102(b) and § 102(e)

Claims 23-31, 33, 45-46, 120-124 and 153-154 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,077,709 to Bennett *et al.* ("Bennett").

Purporting to give applicants' claims their broadest interpretation, the Examiner contends that claim 153, as examined,[1] permits the claimed subsequence to be present in any order. On that basis, the

[1] 153. A compound consisting of 12-50 nucleotides and/or nucleotide analogues, wherein said compound comprises a subsequence of at least 8 nucleotides or nucleotide analogues, said subsequence being located within the sequence ctcaatccatggcagc (SEQ ID NO: 130), and wherein said subsequence comprises at least one nucleotide analogue.

Examiner contends that Bennett teaches an antisense compound targeted to a survivin gene, wherein the compound comprises 18 nucleobases, and has a subsequence of at least 8 nucleotides of applicants' SEQ ID NO: 130. The Examiner particularly points to SEQ ID NO: 1 of Bennett as meeting all of the limitations of claim 153 as broadly interpreted. The Examiner further contends that Bennett teaches compositions comprising pharmaceutically acceptable carriers or diluents and also teaches conjugates of the oligonucleotides. Applicants traverse the rejection.

At the outset, Applicants point out that claims 23-31, 33, 45-46, 120-124 and 153-154 have been canceled and the subject matter incorporated respectively into claims 175-184, 200-201, 221-224 and 170-171. *See* claim correspondence chart, above. Claim 170, from which all of the corresponding new claims either directly or indirectly depend, recites that the region of the claimed oligonucleotide compound comprises at least 8 contiguous monomers and has a sequence that is identically present in SEQ ID NO: 130: ctcaatccatggcagc.

Applicants respectfully point out that Bennett does not disclose an oligonucleotide comprising a region of at least 8 contiguous monomers having a sequence that is identically present in applicants' SEQ ID NO: 130. Applicants respectfully submit that Bennett does not disclose all of the limitations of new claim 170 and therefore, does not anticipate claim 170. In addition, Bennett does not disclose all of the limitations of claims 171, 175-184, 200-201, and 221-224, which depend either directly or indirectly from claim 170, and therefore incorporate all of the limitations of that claim, 37 C.F.R. § 1.75(c). Accordingly, Bennett does not anticipate new claims 170-171, 175-184, 200-201 and 221-224, which correspond to the rejected claims.

Claims 23-31, 33, 45-46, 121 and 153 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,310,044 to Draper *et al.* ("Draper"). Specifically, the Examiner alleges that Draper teaches an oligonucleotide compound comprising at least 8 nucleotides of SEQ ID NO: 130, which is designated as SEQ ID NO: 4 in Draper. The Examiner further contends that Draper teaches oligonucleotides that comprise from 6 to 50 nucleotide analogues, and teaches that the backbone can comprise phosphorothioate linkages. In addition, the Examiner alleges that Draper teaches compositions comprising pharmaceutically acceptable carriers. Applicants traverse the rejection.

At the outset, Applicants point out that claims 23-31, 33, 45-46, 121 and 153 have been canceled, and the subject matter incorporated respectively into new claims 175-184, 200-201, 222 and 170. *See* claim correspondence chart, above. Claim 170, from which all of the corresponding new claims either directly or indirectly depend, recites that the oligonucleotide compound consists of 12-50 monomers

wherein adjacent monomers are covalently linked by a phosphate group or a phosphorothioate group, and that comprises a region of at least 8 contiguous monomers having a sequence that is identically present in SEQ ID NO: 130, and wherein at least one of the monomers in the region is a nucleoside analogue. Draper does not disclose antisense oligonucleotides that have nucleoside analogues, *i.e.,* modified sugar or nucleobase moieties, but only oligonucleotides having modified linkage groups in the backbone. Therefore, Draper does not disclose every limitation of claim 170 and does not anticipate that claim. Furthermore, claims 175-184, 200-201, and 222 depend either directly or indirectly from amended claim 170 and therefore incorporate all of the limitations of that claim. Accordingly, Draper does not anticipate pending claims 170, 175-184, 200-201 and 222.

For the reasons discussed above, Applicants submit that the pending claims are not anticipated by Bennett or by Draper. Reconsideration of the claims and withdrawal of the rejections thereof under 35 U.S.C. §§102(b) and 102(e) is requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 23-31, 33, 45-46, 48-52, 120-124, and 153-159 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Bennett in view of U.S. Patent Publication No. 2003/0032794 to Koch *et al.* ("Koch") and Kurreck *et al.* (2002) *Nucl. Acids Res.* 30(9):1911-1918 ("Kurreck"). In particular, the Examiner contends that Bennett teaches antisense compounds targeted to survivin genes that are 18 nucleobases in length and that comprise a subsequence of at least 8 nucleotides of SEQ ID NO: 130, which according to the Examiner's broadest claim interpretation, do not have to be in the order shown in SEQ ID NO: 130. In addition, Bennett teaches antisense molecules that can comprise nucleotide analogues, compositions comprising pharmaceutically acceptable diluents or carriers, and conjugates of the oligonucleotides with fatty acids and penetration enhancers. Furthermore, the Examiner contends that Bennett teaches compositions comprising chemotherapeutic agents. The Examiner further points out that Bennett does not teach locked nucleic acids for use in the anti-survivin oligonucleotides, but argues that Kurreck teaches antisense oligonucleotides comprising LNAs, LNA "gapmer" oligonucleotides and that LNAs in an oligonucleotide sequence increase the affinity of the oligonucleotides for their targets and their stability. In addition, the Examiner further alleges that Koch teaches that antisense molecules containing LNAs are promising new drug candidates. Therefore, the Examiner argues that it would have been obvious to incorporate LNAs into the compounds of Bennett because Kurreck teaches that such compounds can inhibit gene expression and Koch teaches the desirability of using LNAs in antisense oligonucleotides and how to synthesize them. Applicants traverse the rejection.

At the outset, Applicants respectfully point out that rejected claims 23-31, 33, 45-46, 48-52, 120-124, and 153-159 have been canceled, and the subject matter incorporated respectively into new claims 175-184, 200-205, 221-224 and 170-174, 190, and 194. *See* claim correspondence chart, above.

As discussed above in response to the Examiner's anticipation rejections, claim 170 recites that the region of the claimed oligonucleotide compound comprises at least 8 contiguous monomers, one of which is a nucleoside analogue, and has a sequence that is identically present in SEQ ID NO: 130. Furthermore, pending claims 171-184, 190, 194, 200-205, and 221-224 depend either directly or indirectly from claim 170 and so include the limitation that the claimed oligonucleotides comprises a region of at least 8 contiguous monomers, one of which is a nucleoside analogue, and that has a sequence that is identically present in SEQ ID NO: 130. None of the references cited by the Examiner discloses a region of at least 8 contiguous monomers wherein the sequence of the region is identically present in SEQ ID NO: 130. The oligonucleotide sequences disclosed in Bennett, including SEQ ID NO: 1 pointed out in the Office Action, are for the modulation of survivin genes, but do not comprise at least 8 contiguous monomers having a sequence that is identically present in SEQ ID NO: 130. Furthermore, neither Kurreck nor Koch cures the deficiencies of Bennett, since neither secondary reference discloses such a region. Thus, the Examiner has failed to establish a *prima facie* case of obviousness because none of the cited references, either alone or in combination, discloses every element of the rejected claims. *See* M.P.E.P., 8th ed. § 2143A. Thus, one skilled in the art reading the cited references could not combine all of the elements as claimed to yield a predictable result because all of the elements were not known in the art. Therefore, Applicants respectfully submit that the pending claims are not obvious over the cited combination of references.

Claims 23-31, 33, 45-46, 48-52, 120-124, and 153-159 stand rejected as allegedly being obvious over Draper, Bennett, Koch and Kurreck. Specifically, the Examiner contends that Draper teaches an oligonucleotide compound (SEQ ID NO: 4) comprising at least 8 nucleotides of SEQ ID NO: 130 as claimed in claim 153. Furthermore, Draper teaches that the oligonucleotide compound comprises from 6 to 50 nucleotide analogues, and that the oligonucleotide can comprise phosphate and phosphorothioate linkages. In addition, the Examiner contends that Draper teaches compositions comprising pharmaceutically acceptable carriers, but does not teach compounds comprising analogues such as 2'-methoxyethyl, conjugates, pharmaceutical compositions comprising chemotherapeutic agents, LNAs or "gapmers." The Examiner further alleges that Bennett teaches nucleotide analogues such as 2'-methoxyethyl, phosphate and phosphorothioate linkages, pharmaceutical compositions and conjugates, and compositions containing chemotherapeutic agents. In addition, the Examiner contends that Bennett

teaches compounds comprising at least 8 nucleotide analogues. The Examiner also contends that Kurreck teaches that antisense oligonucleotides comprising LNAs improve affinity for the complementary sequence and the stability of oligonucleotides, and also teaches oligonucleotides that are "gapmers." Furthermore, the Examiner contends that Koch teaches that antisense compounds comprising LNAs are promising new drug candidates, and teaches the preparation of such molecules. Thus, the Examiner argues that it would have been obvious from this combination of references to make compounds comprising nucleotide analogues such as 2'-methoxyethyl, conjugates, and compositions comprising an antisense compound and a chemotherapeutic agent. Furthermore, the Examiner alleges that it would have been obvious from the combination of references to incorporate LNAs into the antisense oligonucleotides of Draper, especially in a "gapmer" configuration. The Examiner contends that one would have been motivated to incorporate nucleotide analogues into the compounds of Draper (which the Examiner alleges teaches that antisense oligonucleotides can modulate the expression of survivin genes) because of the increased affinity for the target and increased stability of the oligonucleotides. Applicants traverse the rejection.

At the outset, Applicants point out that claims 23-31, 33, 45-46, 48-52, 120-124, and 153-159 have been canceled, and the subject matter thereof incorporated respectively into new claims 175-184, 200-206, 221-224 and 170-174, 190 and 194. *See* claim correspondence chart, above. Contrary to the Examiner's contentions in the Office Action at page 13, Draper does not teach antisense oligonucleotides that modulate survivin gene expression, but only discloses antisense oligonucleotides for the modulation and detection of herpes virus genes. Draper discloses that oligonucleotide modifications can enhance penetration into the cells, and discloses specific modifications to the phosphodiester backbone, *i.e.,* replacing it with other linkage groups such as phosphorothioates, alkyl phosphorothioates, N-alkyl phosphoramidates, phosphorodithioates, alkyl phosphonates and short chain alkyl or cycloalkyl structures. *See* Draper, col. 10, line 61-col. 11, line 4. Draper also discloses that antisense oligonucleotides can include modified bases or modified sugars, but does not disclose any specific modifications to the sugar or base moieties of the oligonucleotides. *See* Draper, col. 11, lines 10-15. Thus, Draper does not suggest: (1) the use of antisense oligonucleotides to modulate expression of genes other than herpes virus genes; (2) that any of the disclosed sequences are suitable for or capable of modulation of genes other than herpes virus genes; (3) antisense oligonucleotides with specific nucleoside (*i.e.,* base or sugar) modifications; or (4) the effect of specific nucleoside modifications on the ability of the oligonucleotide to modulate gene expression.

Neither Bennett, Kurreck nor Koch remedies the deficiencies of Draper. Bennett discloses antisense oligonucleotides for the modulation of survivin expression, but does not disclose oligonucleotide compounds comprising a of least 8 contiguous monomers, wherein at least one monomer of the region is a nucleoside analogue and wherein the sequence of the region is identically present in SEQ ID NO: 130, as claimed in claim 170. Furthermore, Bennett does not disclose the use of LNAs in antisense oligonucleotides. Kurreck and Koch disclose the use of LNAs in antisense oligonucleotides, but do not suggest LNA-containing antisense oligonucleotides that comprise a region of at least 8 contiguous monomers, wherein the sequence of the region is identically found in SEQ ID NO.: 130.

Furthermore, as is evidenced by Bennett, the modulation of gene expression by modified antisense oligonucleotides is unpredictable. Bennett determined the % inhibition of survivin gene expression by various antisense oligonucleotides directed to the coding region, the 5'-untranslated region or the 3'-untranslated region of a survivin gene, and having different backbone and/or sugar modifications (*e.g.*, phosphorothioate oligonucleotides versus gapmers having a phosphorothioate backbone and 2'-MOE sugar modifications in the "wing regions" and deoxynucleotides in the center). *See* Bennett, col. 27-col. 28. Of the 80 antisense oligonucleotides tested, only 8 (*i.e.*, 10%) showed greater than 50% inhibition of survivin gene expression. Furthermore, oligonucleotides having the same nucleic acid sequence were found to exhibit vastly different abilities to inhibit survivin gene expression depending on the modifications incorporated into that sequence (*see* SEQ ID NO: 38 – 20% inhibition by phosphorothioate-containing oligonucleotide versus 80% inhibition by gapmer; compare SEQ ID NO: 28 – 64% inhibition by phosphorothioate-containing oligonucleotide versus 27% inhibition by gapmer). *See* Bennett, Table 1 and Table 2, col. 27-28. Thus, Bennett clearly shows that the selection of a target site and of specific modifications to antisense oligonucleotides unpredictably influences the modulation of gene expression.

Accordingly, it would not have been obvious to one skilled in the art to modify the anti-herpes virus oligonucleotide having SEQ ID NO: 4 disclosed in Draper by introducing modified nucleosides as claimed in the pending claims in order to achieve a predictable result of modulating the expression of a gene other than a herpes virus gene.

For the reasons discussed above, Applicants submit that pending claims 170-184, 190, 194, 200-206, and 221-224 are not obvious over Bennett in view of Koch and Kurreck. Furthermore, Applicants submit that pending claims are not obvious over Draper, Bennett, Koch and Kurreck. Accordingly, withdrawal of the rejections thereof under 35 U.S.C. §§103(a) is requested.

Rejections for Non-Statutory Double Patenting

The Examiner has maintained her rejection of claims 3, 5-16, 19-21, 23-38, 45-46, 48-52, 120-124 and 153-169 for obviousness-type double patenting over claims 1-11 of co-pending Application Serial No. 11/272,124. Applicants point out that these claims have been canceled, and the subject matter thereof has been incorporated into new claims 170-206, and 221-224. *See* claim correspondence chart, above. Applicants respectfully request that the Examiner continue to hold this rejection in abeyance until allowable subject matter is found in one of the co-pending cases.

Conclusion

Claims 170-224 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

If there are remaining issues that the Examiner believes could be addressed by conducting an interview or entering an Examiner's Amendment, the Examiner is cordially invited to contact the undersigned to discuss such issues.

No fees beyond those submitted herewith are believed to be due in connection with this Amendment. However, the Director is authorized to charge any additional fees that may be required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (**Order No. 366929-018 US (396515)**.

Respectfully submitted,

Date: May 28, 2008

Anna D. DiGabriele
Reg. No. 59,933

DECHERT LLP
Customer No. 37509
Tel: 650.813.4800
Fax: 650.813.4848

14273270.1.BUSINESS